RECEIVED
CENTRAL FAX CENTER
AUG 1 4 2006

REMARKS/ARGUMENTS

Claims 1, 3-15, 17-28, 58 and 59 are under examination in the application. The Office Action mailed on October 17, 2005, includes the following objections and rejections:

1. Claims 5 and 37 are rejected under 35 U.S.C. § 112 second paragraph;
2. Claim 37 is rejected under 35 U.S.C. § 112 first paragraph;
3. Claims 1-4, 6, 8, 9, 15-17 and 37 are rejected under 35 U.S.C. § 102 as anticipated by Baracchini.
4. Claims 1-4, 6, 8, 9, 15-17 and 37 are rejected under 35 U.S.C. § 102 as being as anticipated by Parrish, et al.

Claim Rejections – Claims 5 and 37 is rejected under 35 U.S.C. § 112, First Paragraph

The Action also rejects claims 5 and 37 under 35 U.S.C. § 112. Claim 5 has been canceled. Claims 1 and 37 as amended fully comply with 35 U.S.C. § 112. Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112.

Claim Rejections – Claim 37 is rejected under 35 U.S.C. § 112, First Paragraph

The Action also rejects claim 37 under 35 U.S.C. § 112 as failing to comply with the enablement requirement. Applicants disagree with the interpretation of Opalinska, et al. The Action states:

> "Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

However, in the same paragraph Opalinska, et al., states that "[n]evertheless, oligonucleotides can escape from the vesicles intact, enter the cytoplasm and then diffuse into the nucleus..." Clearly, this reference discloses that the skilled artisan knew at the time of the present invention that oligonucleotides can diffuse into the nucleus. Opalinska, et al., also states that these techniques have been successfully been used both *in-vivo* and *in-vitro* (see second paragraph page 504). Furthermore, Opalinska, et al., states that "these small molecules have the ability to diffuse into the nucleus where

they can contact dsDNA..." (page 504). In addition, Opalinska, et al., states that nucleic-acid drugs are undergoing clinical trial (e.g., "Nucleic-acid Drugs in the Clinic" page 507), still further clinical trials are listed for numerous oligonucleotide treatments in Table 2 on page 511 of Opalinska, et al. As stated on page 507 of Opalinska, et al., both European and United States authorities approved a nucleic-acid drug for use to treat a viral infection of the eye. Opalinska, et al., clearly supports the knowledge by the skilled artisan in the area of nucleic-acid drugs. Therefore, the claims of the present invention are enabled and clearly within the scope of the skilled artisan.

Based on the known skill in the art, Applicants submit that the claims fully comply with the enablement requirement under 35 U.S.C. § 112. M.P.E.P. § 2164.02 states that "[c]ompliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed" and goes on to explain that "[t]he specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation." *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). In fact, the M.P.E.P. clearly states that "the absence of working examples will not by itself render the invention non-enabled..." as "[a] single working example in the specification for a claimed invention is enough to preclude a rejection which states that nothing is enabled since at least that embodiment would be enabled." The present application includes working examples based on work actually performed. For example, the present application provides different types of gene silencing that may be achieved using the thioaptamers of the present invention, e.g., see [0038-0041] and Table 1. Numerous RNA thioaptamers sequences, synthesis methods for thioaptamers and gene silencing studies are listed in the application, e.g., see [0058-0100] and Figures 7-11. The claims of the present invention are clearly enabled under 35 U.S.C. § 112 given the present application and the knowledge of the skilled artisan. Furthermore, the specification teaches the methods of making, isolating, characterizing and using the full range of thio-modified siRNA aptamers.

Therefore, given the teachings and examples of the present application and the knowledge of the skilled artisan it is clear that the claims fully comply with the enablement requirement under 35 U.S.C. § 112. Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. §112.

Claim Rejections – Claims 1-4, 6, 8, 9, 15-17 and 37 are rejected under 35 U.S.C. § 102(b)

The Action also rejects claims 1-4, 6, 8, 9, 15-17 and 37 under 35 U.S.C. § 102(b) as being anticipated by United States Patent 5,801,154 issued to Baracchini ("Baracchini") which is said to disclose the claimed invention. Applicants submit that Baracchini is non-enabling art and as such cannot anticipate the present invention.

Baracchini discloses antisense oligonucleotides designed to hybridize to the mRNA encoding multidrug resistance-associated protein (MRP) that may have at least one of the intersugar linkages between nucleotides of the oligonucleotide as a phosphorothioate linkage. However, Baracchini does not teach how to make an "at least partially" modified thioaptamer. For example, Baracchini does not teach which linkages to modify, how many linkages to modify and the location of the linkages to be modified and so forth. Baracchini does not (1) teach making an "at least partially" modified thioaptamer; (2) isolating an "at least partially" modified thioaptamer; (3) using an "at least partially" modified thioaptamer nor (4) characterizing an "at least partially" modified thioaptamer. Using Baracchini alone, the present invention could not be constructed without the teaching of the disclosure of the present application.

There are clear differences between the partially modified thioaptamer of the present invention and antisense oligonucleotides designed to hybridize to the mRNA of Baracchini. For example, studies comparing siRNA to chemically optimized antisense technology have indicated that fewer RNA duplexes have to be screened in order to identify active siRNAs, that siRNAs might be more potent inhibitors of gene expression than antisense (Miyagishi, et al., 2003), and that siRNAs were less toxic to cells (Braasch, et al., 2003). Phosphorothioate (PS) modified antisense oligonucleotides are the "gold standard' for antisense therapy, conferring nuclease resistance to these ssDNA oligonucleotides and increasing binding to serum proteins which increases bioavailability (Geary, et al., 2001).

The present invention provides unique abilities of (thio)aptamers to perform their essential functions: (1) they target specific proteins in physiological pathways; (2) their sequence and structure is not intuitively obvious from canonical biologics and oftentimes can only be deduced by combinatorial selection against their targets; and (3) they bind their targets with higher affinities than do naturally occurring nucleic acid substrates. Importantly, the backbone modifications of

thioaptamers and their nucleic acid backbone analogs enable aptamers to be introduced directly into living systems with in vivo lifetimes many times greater than unmodified nucleic acids, due to the inherent nuclease resistance of the modified aptamers. The inherent nuclease resistance is extraordinarily important for their efficacy in use.

Applicants respectfully submit that claims 1-4, 6, 8, 9, 15-17 and 37 as amended are not anticipated by Baracchini because Baracchini is non-enabling art and as such cannot anticipation the present invention. Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 102(b).

Claim Rejections – Claims 1-4, 6, 8, 9, 15-17 and 37 are rejected under 35 U.S.C. § 102

The Action also rejects claims 1-4, 6, 8, 9, 15-17 and 37 under 35 U.S.C. § 102(b) as being anticipated by Parrish, et al. (Molecular Cell 2000) ("Parrish"). Applicants respectfully submit that the cited reference fails to meet the standard of 35 U.S.C. § 102(b) namely, teaching all elements of the claimed invention either explicitly or impliedly and every limitation of the present invention. Even if Parrish did possess every limitation of the present invention Parrish is non-enabling and as such still cannot anticipation the present invention.

Parrish does not meet the standard of 35 U.S.C. § 102(b) namely, teaching all elements of the claimed invention. Parrish does not teach a partially thio-modified thioaptamer that mediates gene silencing. At best, Parrish merely discloses, but does not enable, a dsRNAi having all of one nucleotide in a sequence modified.

Simply, Parrish is non-enabling. Parrish does not teach a thioaptamer with a perfect or imperfect complementarity match to a target gene. To the contrary, Parrish teaches that sequence and motifs are unimportant as they "...were able to rule out a specific requirement for any sequence motif in the trigger or target RNA and were able to rule out any requirement for A, U, or C residues in the fragment sequence" (page 1083 column 1). Additionally, Parrish indicates that the short RNAs may have no role in RNAi and may simply be a product of RNAse digestion (page 1084 column 2). The data from the dsRNAi experiments of Parrish (page 1078 column 2) indicates that the smaller dsRNAi required 250 times the concentration of the larger dsRNAi. Furthermore, the sequences listed in Parrish contain 3 of the 4 nucleotides, e.g., see Figure 1B. Simply, Parrish does not teach an isolated

thioaptamer that mediates gene silencing having a partially thiomodified phosphodiester backbone with one or more of the following rATP(αS), rUTP(αS), rGTP(αS), rCTP(αS), rATP(αS_2), rUTP(αS_2), rGTP(αS_2) or rCTP(αS_2).

Applicants respectfully submit that claims 1-4, 6, 8, 9, 15-17 and 37 as amended are not anticipated by Parrish. Parrish is non-enabling and as such cannot anticipation the present invention. Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 102(b).

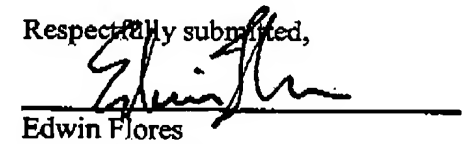
Conclusion

In light of the remarks and arguments presented above, Applicants respectfully submit that the claims in the Application are in condition for allowance. Favorable consideration and allowance of the pending claims is therefore respectfully requested.

If the Examiner has any questions or comments, or if further clarification is required, it is requested that the Examiner contact the undersigned at the telephone number listed below.

Dated: August 14, 2006

Respectfully submitted,



Edwin Flores
Registration No. 38,453
ATTORNEY FOR APPLICANTS

Customer No. 34,725
CHALKER FLORES, LLP
2711 LBJ Freeway Suite 1036
Dallas, TX 75234
214.866.0001 Telephone
214.866.0010 Facsimile

ESF/cps